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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/558,948	11/30/2005	Roberto Golzi	EURA-028/00US 307853-2054	6650

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EXAMINER	
WELTER, RACHAEL E	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
05/13/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zpatdcdocketing@cooley.com

Office Action Summary	Application No.	Applicant(s)	
	10/558,948	GOLZI ET AL.	
	Examiner	Art Unit	
	RACHAEL WELTER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 24-38* is/are pending in the application.

4a) Of the above claim(s) *1-21 and 27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24-26 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/7/11 has been entered.

Claim Status

Claims 1-22 and 24-38 are pending. Claims 22, 24-26 and 33-38 are drawn to the elected species. Claims 1-21 and 27-32 are withdrawn. Claim 23 is cancelled.

Withdrawn Rejections

The rejection of claim 24 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the examiner's reconsideration.

The rejection of claims 22, 24-25, and 38 rejected under 35 U.S.C. 102(b) as being anticipated by Tsuchida et al (US 6,558,700; Published 5/6/2003) is withdrawn in light of applicant's amendments.

The rejection of claims 33-34 rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuchida et al (US 6,558,700; Published 5/6/2003) in view of Banakar ("Pharmaceutical Dissolution Testing," Volume 49, 1992, pg. 144) is withdrawn in light of applicant's amendments.

The rejection of claim 35 rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuchida et al (US 6,558,700; Published 5/6/2003) in view of Breitenbach et al (US Patent No. 6,120,802) is withdrawn in light of applicant's amendments.

The rejection of claims 26 and 36-37 rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuchida et al (US 6,558,700; Published 5/6/2003) in view of Hsaio (US Patent No. 4,634,587; Published 1/6/1987) and Alderman (US Patent No. 4,704,285; Published 11/3/1987) is withdrawn in light of applicant's amendments.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22, 24-25, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuchida et al (US 6,558,700; Published 5/6/2003) in view of McKetta et al (Encyclopedia of Chemical Processing and Design, "Organic Phase Separation Coacervation," pg. 167, 1989).

Tsuchida et al teach granules comprising a core particle and a matrix layer comprised of a water-insoluble polymer and active ingredient for coating said core particle (column 2, lines 7-10). The water insoluble polymer is preferably ethyl cellulose (column 2, lines 16-17). According to Tsuchida et al, it is essential that the water-insoluble polymer be dissolved in such a solvent and that an active ingredient be dissolved or uniformly dispersed in the water insoluble polymer solution (column 3, lines 2-5). When the active ingredient is of dispersed form, it is preferably below 20 um for improving adhesion to a core particle, securing uniformity, and performing sufficient

stirring for establishing uniformity (column 3, lines 6-9). The present invention may be applied to various active ingredients including water-soluble drugs, such as phenylpropanolamine hydrochloride (column 3, lines 10-14; Table 1). An average particle diameter of the core particle ranges preferably between 100-1000 um (column 4, lines 11-12). In example 4, the amount of drug is in an amount of approximately 22 wt.% and in examples 1 and 2, ethyl cellulose is in an amount of approximately 25 wt.% (see Table 1; column 7, lines 50-65). The matrix granules can be additionally coated with a release-controlling film comprising ethyl cellulose (see Table 1; column 2, lines 24-26).

Tsuchida et al do not teach a coacervated polymeric membrane coating.

McKetta et al teach that coacervation is widely used in the pharmaceutical industry for coating small particles, especially with the water-insoluble polymer, ethylcellulose. According to McKetta et al, phase separation coacervation is useful for coating particles ranging in size from a few microns to 1 cm, and can be used to form walls of varying thicknesses and high integrity.

Therefore, it would have been obvious to apply the matrix layer of Tsuchida et al comprising ethylcellulose by coacervation, as suggested by McKetta et al. One would have been motivated to do so with a reasonable expectation of success since McKetta et al suggest that coacervation is widely used in the pharmaceutical industry for coating small particles with ethylcellulose for varying degrees of thickness and integrity.

Regarding the amount of drug and coating polymer (i.e. ethylcellulose), it is noted that the amount of drug and coating polymer in Tsuchida's microcapsules nearly

touches the instant ranges. According to MPEP 2144.05, "A prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Furthermore, it is the examiner's position that it would have been obvious to manipulate the amounts during routine optimization. One would have been motivated to do so depending on the desired "strength" of the composition, the particular drug being administered, the desired release rate, the patient's medical history, and the length of time the patient has been on the drug. Drug concentration and controlled release coatings are result-effective variables, i.e., variables which achieve a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie,* 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

Claims 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuchida et al (US 6,558,700; Published 5/6/2003) in view of McKetta et al (Encyclopedia of Chemical Processing and Design, "Organic Phase Separation Coacervation," pg. 167, 1989) as applied to claims 22, 24-25, and 38 above and in further view of Banakar ("Pharmaceutical Dissolution Testing," Volume 49, 1992, pg. 144).

The disclosures of Tsuchida et al and McKetta et al are discussed above.

Although Tsuchida et al teach active ingredient particles preferably below 20 um for improving adhesion to a core particle, securing uniformity and performing sufficient stirring for establishing uniformity, Tsuchida et al do not anticipate the active ingredient particle size. Instead, Tsuchida et al teach a particle size that encompasses and overlaps the instant active ingredient particle size.

According to MPEP 2144.05, in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).* Additionally, it would have been obvious to an artisan of ordinary skill at the time the invention was made to manipulate and optimize the particle sizes of the active ingredients. Optimization of parameters is a routine practice that would be obvious to a person of ordinary skill in the art to employ and reasonably expect success. One would have been motivated to determine the optimal size of each active ingredient particle in order to best achieve the desired results. See *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) &* MPEP 2144.05. Burden is on applicant to prove the criticality of the claimed range.

Furthermore, Banakar teaches that reduction in particle size of drugs contained in tablets or capsules will enhance dissolution and absorption, which can be attributed to tablet production.

Therefore, it would have been obvious to an artisan of ordinary skill at the time the invention was made to reduce the particle size of the active ingredients contained within the pharmaceutical compositions of Tsuchida et al. One would have been

motivated to do so depending on the desired dissolution rate and bioavailability of the drug. More specifically, one would have been motivated to reduce the particle size of the active ingredients of Tsuchida et al in order to achieve a higher dissolution rate and enhanced absorption.

Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuchida et al (US 6,558,700; Published 5/6/2003) in view of McKetta et al (Encyclopedia of Chemical Processing and Design, "Organic Phase Separation Coacervation," pg. 167, 1989) as applied to claims 22, 24-25, and 38 above and in further view of Breitenbach et al (US Patent No. 6,120,802).

The disclosures of Tsuchida et al and McKetta et al are discussed above.

Tsuchida et al and McKetta et al do not anticipate a core that constitutes 50-95 wt.% of the microcapsule.

Breitenbach et al teach a method of producing multi-layer medicaments in solid form for oral or rectal administration. At least one of the layers has an active agent and another embodiment has the active in the outer layers and inner layers (column 2, line 59 -column 3, line 5). Breitenbach et al teach that the thickness of the layers can be chosen depending on the required release characteristics and that the release can be delayed by increasing the thickness of the layers (column 3, lines 6-9).

Therefore, it would have been obvious to an artisan of ordinary skill at the time the invention was made to increase the core and use less coating in the matrix granules of Tsuchida et al. One would have been motivated to do so since Breitenbach et al

teach that less coating (i.e., more core) would mean a less delayed release of the active. Thus, it would have been within the skill of an artisan to increase the core if one desired a bulkier granule and a more immediate release rate.

Claims 26 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuchida et al (US 6,558,700; Published 5/6/2003) in view of McKetta et al (Encyclopedia of Chemical Processing and Design, "Organic Phase Separation Coacervation," pg. 167, 1989) as applied to claims 22, 24-25, and 38 above and in further view of Hsaio (US Patent No. 4,634,587; Published 1/6/1987) and Alderman (US Patent No. 4,704,285; Published 11/3/1987).

The disclosures of Tsuchida et al and McKetta et al are discussed above.

Tsuchida et al and McKetta et al do not teach the addition of water-soluble additives in its ethylcellulose coating. However, it is noted that Tsuchida et al teach that its coatings can comprise water-insoluble polymers either alone or in combination (column 2, lines 53-54). Tsuchida et al additionally teach that it is feasible to freely control dissolution rate of the active ingredient, considering its solubility in water, according to the type of the water-insoluble polymer forming the matrix granule (column 3, lines 26-29).

Hsaio teaches a sustained release quindine dosage form made from a plurality of pellets (abstract). The pellets comprise a coating containing a 5-15 wt.% mixture of ethylcellulose and hydroxypropylcellulose (column 1, lines 41-64). According to Hsaio, the presence of 20-40 wt.% of hydroxypropylcellulose in the coating provides channels

for the water to enter and allow the active ingredient to leach out of the dosage. As evidenced by the instant specification, hydroxypropylcellulose is a water-soluble additive (pg. 6, lines 4-6).

Alderman teaches solid tablets comprising fine particle sized hydroxypropyl cellulose ether (abstract). Alderman teaches that the particle size of the HPC is sufficient when at least 70 wt.% can pass through a 100 mesh screen, which corresponds to less than 140 um (column 2, lines 49-55). According to Alderman, when the particle size is sufficiently fine, the release of the active ingredient from a solid tablet is delayed longer upon contacting an aqueous acid environment compared to a tablet formulated with a chemically identical but coarser particle sized HPC (column 2, lines 41-46).

Therefore, it would have been obvious to an artisan of ordinary skill at the time the invention was made to add water-soluble additives to the ethylcellulose coatings of Tsuchida et al. One would have been motivated to do so since Tsuchida et al teach that dissolution rates can be controlled by the ingredients in its ethylcellulose coatings and Hsaio teaches that hydroxypropylcellulose provides a more water-soluble coating and thus a more immediate release. More specifically, one would have been motivated to provide HPC with a finer particle size than 140 um since Alderman teaches that finer hydroxypropylcellulose provides a more delayed release. Thus, depending on the desired release rate of the matrix granules, it would have been within the skill of an artisan to add water-soluble additives in the claimed particle sizes in the ethylcellulose coating of Tsuchida et al.

Response to Arguments

With respect to applicant's amendment, "coacervated" polymeric membrane, it is noted that the examiner supplemented the rejections above with the new reference, McKetta. It is the examiner's position that McKetta renders obvious coacervating the polymeric membrane of Tsuchida. As such, applicant's arguments regarding this limitation are moot in view of the new ground(s) of rejection above.

Applicant further argues in the arguments filed 2/7/11 that the instant claims require the active ingredient to be present in amounts ranging from 0.2-21 wt.% with respect to the weight of the microcapsule. Applicant notes that Tsuchida's examples 1-5 are well above the maximum value of 21%.

In response to applicant's arguments, it is noted that if one includes the ethyl cellulose coating film in example 4 (see Table 4 of Tsuchida), the drug concentration is in an amount of 22 wt.%. According to MPEP 2144.05, "A prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Furthermore, it is the examiner's position that it would have been obvious to manipulate the drug concentration during routine optimization. One would have been motivated to do so depending on the desired "strength" of the composition, the particular drug being administered, the desired release rate, the patient's medical history, and the length of time the patient has been on the drug. Drug concentration is a

result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie,* 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

Applicant further argues that Banakar, Breitenbach, Hsaio, and Alderman fail to remedy the deficiencies of Tsuchida.

In response to applicant's arguments over the secondary references, it is noted that the examiner addressed applicant's arguments regarding Tsuchida above, which is incorporated herein. Banakar, Breitenbach, Hsaio, and Alderman were only cited as motivation to reduce the active's particle size, make a bulkier core, and add additives in the polymeric membrane respectively. Since applicant has not argued these secondary teachings, it is the examiner's position that the rejections should be maintained for the reasons stated above.

Conclusion

Claims 22, 24-26 and 33-38 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RACHAEL WELTER whose telephone number is (571)270-5237. The examiner can normally be reached 7:30-5:00 Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

REW

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611